EXHIBIT B

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re application of: | Confirmation No.: 4326 |
| HO *et al.* | Art Unit: 1651 |
| Appl. No.: 09/960,244 | Examiner: Leon B. Lankford, Jr. |
| Filed: September 21, 2001 | Atty. Docket: 2560.0020000/JAG/D-S |
| For: **Cell Populations Which Co-Express CD49c and CD90** | |

## Supplemental Amendment and Reply Under 37 C.F.R. § 1.111(a)(2)(B)

***Mail Stop Amendment***

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

In further reply to the Office Action mailed October 5, 2007, Applicants' interview with the Examiner on April 3, 2008, and the Examiner's email correspondence of June 11, 2008, Applicants submit herein a claim amendment (new claim 97), as suggested by the Examiner, and discuss why this claim should be allowed.

Amendments to the Claims begin on Page 2.

Remarks begin on Page 4.

Exhibits A through G are attached hereto.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefore (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

***Amendments to the Claims***

**The listing of claims will replace all prior versions, and listings of claims in the application.**

1-13. (Cancelled).

14. (Previously Amended) An isolated cell population derived from human bone marrow, wherein greater than about 91% of the cells of the cell population co-express CD49c and CD90, and wherein the cell population maintains a doubling rate of less than about 30 hours after 30 cell doublings.

15-20. (Cancelled).

21. (Previously Amended) The isolated cell population of Claim 14, further including expression of p21 or p53 after between about 20 to about 50 population doublings of the cells, wherein expression of p53 is a relative expression of up to about 3000 transcripts of p53 per $10^6$ transcripts of an 18s rRNA and expression of p21 is a relative expression of up to about 20,000 transcripts of p21 per $10^6$ transcripts of an 18s rRNA.

22-24. (Cancelled).

25. (Previously Amended) The isolated cell population of Claim 14, wherein the cell population does not express CD34 and/or CD45.

26. (Previously Amended) The isolated cell population of Claim 14, wherein the cell population further expresses at least one trophic factor selected from the group consisting of BDNF, IL-6, NGF and MCP-1.

27-96. (Cancelled).

97. (New) An isolated cell population obtainable from human bone marrow by steps that comprise:

a) incubating human bone marrow cells under a low oxygen condition such that said cells when allowed to adhere to a tissue culture-treated surface will produce adherent colony forming units (CFU); and,

b) passaging cells in said adherent CFU at a seeding density of less than about 2500 cells/$cm^2$,

wherein greater than about 91% of said passaged cells co-express CD49c and CD90, and wherein said passaged cells maintain a population doubling rate of less than about 30 hours after 30 cell doublings.

## *Remarks*

In response to Applicants' interview with the Examiner on April 3, 2008, and in response to the Examiner's email correspondence of June 11, 2008, Applicants respectfully request that the present *Supplemental Amendment and Reply* be entered and considered (along with the *Amendment and Reply* and other documents submitted by Applicants on March 5, 2008) in response to the Office Action mailed Oct. 5, 2007.

Applicants respectfully submit that the claims presented herein should be allowed based on the specification and claims as originally filed and based on the explanations, arguments, evidence and affidavits previously submitted in replies to office actions in the present application. New claim 97 is submitted herein as a follow-up to Applicants' interview with the Examiner on April 3, 2008 and in response to the Examiner's email correspondence of June 11, 2008. In particular, during an April 3, 2008 interview with the Examiner, the Examiner agreed to consider the allowability of a product-by-process claim in response to the currently pending office action in the present application. Additionally, in a June 11, 2008 email from the Examiner, the Examiner requested that Applicants submit a *formal* amendment in place of the informally proposed claim amendment previously submitted for the Examiner's consideration on April 30, 2008. Additionally, the Examiner's June 11th email message requested "a discussion on why this claim should be allowed." Accordingly, Applicants submit herewith a formal *Supplemental Amendment and Reply* to enter the previously proposed product-by-process claim (new claim 97) along with a discussion on why this claim should be allowed.

### *Allowance of New Product-By-Process Claim 97*

Applicants note that new claim 97 finds support in the present application as originally filed. For example, support for claim 97 can be found in the specification at: page 11, line 12 to page 12, line 5; and, Examples 1 through 4, page 25 to page 30.

Furthermore, Applicants submit that new claim 97 should be allowed because the prior art does not teach or suggest that a combination of:

1) incubating human bone marrow cells under a low oxygen condition such that said cells form adherent cell colonies (CFU); *and*,

2) passaging the adherent cell colonies obtained at a seeding density of less than about 2500 cells/$cm^2$

would produce an isolated population of human bone marrow cells wherein greater than about 91% of said passaged cells co-express CD49c and CD90, and wherein said passaged cells maintain a population doubling rate of less than about 30 hours after 30 cell doublings.

Indeed, the prior art does not teach or suggest that applying a combination of low oxygen concentration and low cell density passaging to the isolation and culturing of human bone marrow cells would produce the unique population of cells that Applicants have obtained via the process recited in claim 97. In other words, obtaining the presently claimed unique, isolated population of human bone marrow cells by combining low oxygen conditions and low cell density culturing is a novel, as well as a surprising and unexpected result.

Hence, Applicants particularly submit that no publications previously cited by the Examiner[1] nor any prior art of which Applicants are currently aware teaches or suggests isolation of, or the possibility of isolating, the unique cell population of claim 97. Moreover, the prior art does not teach, suggest, or motivate one of skill in the art to try to obtain, or to expect that one could obtain, the presently claimed unique cell population via a combination of low oxygen condition and low cell density passaging as recited in claim 97. In particular, Applicants note that the human bone marrow cell population so obtained is one wherein the cells express, *inter alia*, CD13, CD44, CD49c, CD90, HLA Class-1 and β (beta) 2-Microglobulin, but do not express, *inter alia*, CD10, CD34, CD45, CD62L, or CD106. *See*, Specification as originally filed as well as Exhibits and Declarations Under 35 U.S.C. § 132 submitted in the present application on May 18, 2007 and March 5, 2008. None of the cells of the prior art have all of these characteristics. These characteristics, while not mentioned in the claims, are inherent in the cells prepared by

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1 *See, for example*: Haynesworth *et al.*, U.S. Patent 5,733,542; Pittenger *et al.*, *Science 284*:143-147 (1999); Woodbury *et al.*, *J. Neurosci. Res. 61*: 364-370 (2000); Lee *et al.*, *Hepatology 40*: 1275-1284 (2004); Jiang *et al.*, *Nature 418*:41-49 (2002); Furcht *et al.*, U.S. Patent 7,015,037; Caplan *et al.*, U.S. Patent 5,486,359; Caplan *et al.*, U.S. Patents 5,811,094; and, Caplan *et al.*, U.S. Patent 5,837,539.

the steps that are claimed in claim 97. Accordingly, Applicants respectfully submit that the product-by-process claim of new claim 97 is fully supported by the specification as originally filed and should be allowed in view of the prior art.

***"Seeding Density"***

On a different but currently pertinent topic, Applicants note that new claim 97 refers to a cell "*seeding density*" of less than about 2500 cells/cm$^2$. In this regard, the Examiner recently issued a rejection in one of Applicants' related patent applications[2], wherein the phrase "seeding density of less than about 30 cell/cm$^{2}$" was rejected as allegedly indefinite under 35 U.S.C. § 112, second paragraph. *See*, Paper No. 20080414, page 2, last paragraph (mailed 05/23/2008 in U.S. Application No. 11/054,824). In particular, the Examiner stated:

> The limitation "seeding density of less than about 30 cell/cm$^{2}$" renders the claims indefinite because density *must be measured* as mass/volume and the cited phrase is "__/area." Therefore, the amount of cells to be used in the instant invention is unclear and the intended claim coverage is indefinite.

*Id* (emphasis added).

Applicants respectfully disagree and traverse this rejection on the basis that "seeding density" is, indeed, properly defined as *per unit area*. *See, e.g., The New College Edition of The American Heritage Dictionary of the English Language, Ed.* William Morris, Houghton Mifflin Co., Boston, MA, p. 353 (1976) which defines "density" as:

1. *The degree or a measure of the degree to which anything is filled or occupied.*
2. Physics.
   a) *The amount of something per unit measure, especially per unit* length, *area*, or volume.
   b) *The mass per unit volume of a substance under specified or standard conditions of pressure and temperature. Also called "mass density."*
3. The number of inhabitants per unit geographical region. Also called "population density".

[2] *See*, U.S. Application No. 11/054,824.

*See*, Exhibit A (emphasis added).

Based on the above-cited rejection, however, the Examiner indicated that to meet the requirements of 35 U.S.C. § 112, second paragraph, new claim 97 *must* define "density" according to the *Examiner's* particularly selected definition (*i.e.*, "mass density") which is one of at least seven possible definitions (three of which are shown above; *i.e.*, definition 2.b). *See*, Exhibit A. In contrast, it is, and would be, readily apparent to those of ordinary skill in the art that the presently pending specification (and new claim 97) refers to "cell density" and "seeding density" in a manner consistent with commonly understood definitions 1. or 2.a) from the above-referenced dictionary. Furthermore, Applicants submit herewith **Exhibits B through G** to show that "cell density" and "seeding density" specified as a number of cells per unit area (*e.g.*, cells/cm$^2$) is a term that has long been used, and is readily understood, by those in the field of cell biology. In particular, **Exhibits B through G** show abstracts from a sampling of six publications ranging from 1981 to 2000 wherein cell density is specified according to the number of cells seeded per unit area (*i.e.*, per/cm$^2$). Finally, the specification as originally filed also teaches that "A seeding density would be the number of adherent cells per cm$^2$ obtained from mononuclear bone marrow cells." *See*, Specification, page 12, lines 8-9.

Thus, with respect to use of the term "seeding density" in claim 97, Applicants submit that this term is used in a manner consistent with a commonly used dictionary definition, in a manner routinely understood by those of ordinary skill in the art, and in a manner consistent with the definition provided in the specification as originally filed. Therefore, Applicants submit that a rejection of new claim 97 under 35 U.S.C. § 112, second paragraph, would be improper.

***Application Pendency***

Applicants also note that the present application has now been pending for almost seven years. As such, Applicants point out that in situations such as this the Examiner and the Examiner's Supervisor are to consider the application "special" and to expedite prosecution to a final disposition:

> **707.02 Applications Up for Third Action and 5-Year Applications**
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> The supervisory patent examiners should impress their assistants with the fact that the shortest path to the final disposition of an application is by finding the best references on the first search and carefully applying them.
>
> The supervisory patent examiners are expected to personally check on the pendency of every application, which is up for the third or subsequent Office action with a view to finally concluding its prosecution.
>
> Any application that has been pending five years should be carefully studied by the supervisory patent examiner and every effort should be made to terminate its prosecution. In order to accomplish this result, the application is to be considered "special" by the examiner.

*See*, M.P.E.P. § 707.2, *Eighth Ed.,* Rev-d Sept. 2007.

Based on the foregoing *Supplemental Amendment and Reply* and the *Amendment and Reply* submitted on March 5, 2008 in response to the currently pending Office Action (as well as all previously filed responses, explanations, arguments, evidence, and affidavits) Applicants respectfully request that all outstanding rejections and objections be withdrawn and that previously amended claims 14, 21, 25, 26 and new claim 97 be considered and passed to allowance.

## *Conclusion*

All of the stated grounds of rejection and objection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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